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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,581	REDDY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,8* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-14 are currently pending and present for examination in this application.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants have not provided a paper copy of the sequences. See particularly 37 CFR 1.821(d).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites three parts under part (b). However, part (ii) under part (b) ends in a

period and therefore it is not clear to the Examiner as to whether part (iii) is claimed as an alternative for parts (i) and (ii) or whether it is indeed part of claim 1 at all rendering it indefinite.

Claims 1, 2, 6, 11 and claims 3-5, 7-10 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 2 6 and 11 are all drawn to a method of screening a test substance for COX-2 inhibitory activity by contacting the test substance with indicator cells and determining the level of proliferation of the indicator cells or decreased level of prostaglandin or increased level of arachidonic acid in the medium. As applicants appear to determine the inhibition COX-2 activity, indirectly by measuring parameters which could be due to the test substance itself, it is not clear to the Examiner as to how applicants will differentiate the inherent effect of the test substance itself (if it has any) from the effect due to inhibition of COX-2. In other words without setting up a set of control reactions and comparing the results with results of test reactions it is not clear to the Examiner as to how applicants can conclude that a given test substance has the desired property of inhibiting COX-2.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step/s is/are explained below. Claims 1-14 are drawn to a method of screening a test substance for COX-2 inhibitory activity comprising contacting the test

substance with indicator cells (which constitutively express endogenous COX-2 or inducibly express endogenous COX-2 or wherein the cells express a GTPase-deficient mutant form of Gα12 (Gα12QL) which mutant has the capacity to induce the production of arachidonic acid and COX-2) and determine (i) level of proliferation of the indicator cells, (ii) level of prostaglandins produced, (iii) level of accumulation of arachidonic acid, wherein a decrease in the proliferation and level of prostaglandins and an increase in the accumulation of arachidonic acid indicates that the test substance has COX-2 inhibitory activity. However, the method lacks the important step of confirming or determining that the proliferation of said indicator cells, or increase in the level of prostaglandins or the accumulation of arachidonic acid is essentially due to the result of COX-2 induction and not due to any other reason during the conduct of the test. There are a number of COX-2 inhibitors already available in the art. It is not clear to the Examiner as to how those skilled in the art would be able to differentiate the identified compound as a specific COX-2 inhibitor which specifically inhibits COX-2 that was specifically induced by the mutant Gα12. Applicants have not provided any step to confirm that they are specifically screening for a COX-2 inhibitor that has been induced specifically by mutant G12. Without such a step the above method would read on any of the existing screening test for COX-2 inhibitors available in the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a method of determining a test substance as a COX-2 inhibitory agent, wherein said COX-2 is induced by a mutant GTPase-deficient Gα12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2-14 are so broad as to encompass any or all other methods of screening for COX-2 inhibitors. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the number of methods broadly encompassed by the claims. Since applicant's claims are specifically directed to a method of screening for COX-2 inhibitor, wherein COX-2 is induced specifically by a mutant Gα12 (and not due to any other stimulus or factor), those skilled in the art will require a knowledge of and guidance with regard to confirming that COX-2 was indeed induced by the mutant G12 gene through an additional step in the method. However, in this case the disclosure does not provide any such step in the method to confirm that COX-2 was indeed induced by the mutant G12. Therefore, it would require undue experimentation of the skilled artisan to determine and confirm that indeed COX-2 was induced by the mutant G12 to make and use the claimed method. The specification provides no

guidance with regard to the above step. In view of the great breadth of the claim, amount of experimentation required to determine that COX-2 was induced by mutant G12, the lack of guidance, working examples, and unpredictability of the art in predicting that COX-2 was induced by the mutant G12, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

The specification does not support the broad scope of the claims which encompasses all methods of screening for COX-2 inhibitors, because the specification does not establish: (A) a step in the above method to link the induction of COX-2 and the mutant G12 by a confirming assay; (B) a step in the above method to confirm that the proliferation of indicator cells is indeed due to the induction of COX-2 by the mutant G12; (C) a step in the above method to confirm that the increased production of prostaglandins by the indicator cells is indeed due to the induction of COX-2 by the mutant G12; (D) a step in the above method to confirm that the accumulation of arachidonic acid by the indicator cells is indeed due to the induction of COX-2 by the mutant G12; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method that lacks a confirmation step. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of proliferation of indicator cells, production of increased prostaglandins and accumulation of arachidonic by indicator cells as due

to the induction of COX-2 by a mutant G12 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by Sheng et al. (J. Clinical Investigation, 1997, Vol. 99(9):2254-2259). Claim 1 is drawn to a method of screening a test substance for COX-2 inhibitory activity by contacting a test substance with indicator cells which express COX-2 constitutively or inducibly and determining the proliferation, or prostaglandin or levels of arachidonic acid. Sheng et al. disclose such an assay by contacting a cell expressing COX-2 with a test substance and determining that said agent decreased the cell proliferation and levels of prostaglandins when compared to control cell which were not treated with said substance. Therefore, Sheng et al. anticipate claim 1 as written.

Claims 2-3, 6-8, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sheng et al. (J. Clinical Investigation, 1997, Vol. 99(9):2254-2259). Claims 2-3, 6-8 are drawn to a method of screening a test substance for COX-2 inhibitory activity by contacting a test substance with indicator cells and determining the proliferation, prostaglandin levels, wherein the indicator cells express a GTPase-deficient mutant

form of Gα12 wherein the mutation is Q229L, which mutant has the capacity to induce the production of arachidonic acid and COX-2 in the indicator cells, and wherein a decrease in the proliferation and prostaglandin levels indicate that the test substance has COX-2 inhibitory activity. Sheng et al. disclose such an assay by contacting a indicator cell expressing COX-2 with a test substance and determining that said agent decreased the cell proliferation and levels of prostaglandins when compared to control cell which were not treated with said substance. Therefore, Sheng et al. anticipate claims 2-14 as written. Sheng et al. do not teach that the indicator cells express a GTPase-deficient mutant form of Gα12 which mutant has the capacity to induce the production of arachidonic acid and COX-2 in the indicator cells. However, as Sheng et al. clearly disclose that several researchers including themselves have consistently reported that colon cancer cells express high levels of COX-2, Examiner takes the position that such high levels observed by Sheng et al. was inherently due to the expression of a GTPase-deficient mutant form of G12, Gα12QL, which mutant has the capacity to induce production of arachidonic acid and COX-2 levels and therefore the indicator cells disclosed in the instant application and the cells disclosed by Sheng et al. are one and the same. Since the Office does not have the facilities for examining and comparing applicants' indicator cells with the cells of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the cells of the prior art does not possess the same material structural and functional characteristics of the claimed indicator cells). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-5, 9-14 rejected under 35 U.S.C. 103(a) as being unpatentable over Sheng et al. as applied to claims 2-3, 6-8 above, and further in view of Dubois et al. (FASEB J., 1998, Vol. 12:10631073) and the common knowledge in the cell biology and immunobiology techniques in the art. Claims 4-5, 9-14 are drawn to method of determination of cell proliferation by tritium labeled thymidine up-take assay, determination of prostaglandin assay by immunoassay and also to a method of screening a test substance for COX-2 inhibitory activity by contacting a test substance with indicator cells and determining the level of arachidonic acid that accumulates in the medium, wherein the indicator cells express a GTPase-deficient mutant form of Gα12 wherein the mutation is Q229L, which mutant has the capacity to induce the production of arachidonic acid and COX-2 in the indicator cells, and wherein an increase arachidonic acid levels when compared to the control reactions, indicate that the test substance has COX-2 inhibitory activity.

The reference of Sheng et al. as it applies to claims 2-3, 6-8 has been discussed above. The reference does no disclose that tritium labeled thymidine uptake assay for the determination of proliferation of cells or the immunoassay for determination of levels of prostaglandins. Similarly, while the reference of Sheng et al. even though discloses that COX is the key enzyme that is primarily responsible for conversion of arachidonic acid to prostaglandins, the reference does not disclose that accumulation of high levels of arachidonic acids is indicative of COX

inhibition nor does it disclose such levels can be monitored by using tritium labeled arachidonic acid in the cell medium.

Dubois et al. teach in general the involvement of COX-2 in a variety of human disorders. The reference clearly teaches that arachidonic acid is converted to various prostaglandins by COXs and that NSAIDS which inhibit COXs leads to increase in arachidonic accumulation(see figure 1).

Therefore, with the teachings of Sheng et al. in hand along with the common knowledge available in the art and the teachings of Dubois et al., it would have been obvious to one of ordinary skill in the art to use tritium labeled thymidine uptake assay to determine the decrease in cell proliferation. One of ordinary skill in the art would have been motivated to do so as this technique is considered fool-proof technique to demonstrate reduction in cell growth. One of ordinary skill in the art would have had a reasonable expectation of success since Sheng et al. already teach a large part of the assay and the thymidine uptake assay is a time tested assay used by a number of inventors. Similarly it would have been obvious to one of ordinary skill in the art to confirm the increase in the prostaglandin levels by doing an immunoassay as such assays are more common in the art and have been highly standardized in the art. One of ordinary skill in the art would have been motivated to do so due to the high reliability of the assay. One of ordinary skill in the art would have a reasonable expectation of success since such assays have been standardized in the art. With the teaching of Sheng et al. either alone or in combination with the reference of Dubois et al. it would have been obvious to one of ordinary skill in the art to do the above assay either by measuring the levels of prostaglandins formed or by the accumulation of the arachidonic acid. One of ordinary skill in the art would have been motivated

to measure the accumulation of arachidonic acid due to the simplicity of such an assay done by simple addition of thymidine labeled arachidonic to the medium followed by counting the radioactive counts after the experiment. One of ordinary skill in the art would have a reasonable expectation of success since such measuring of radioactive counts is routine technique in a laboratory.

Therefore the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao, Ph.D.
June 7, 2003

MANJUNATH RAO
PATENT EXAMINER